CASE REPORT

Hypercalcaemia of malignancy: two primaries in the same patient

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Accepted 30 May 2014

SUMMARY

Hypercalcaemia of malignancy (HCM) is a grave emergency in a cancer patient. Metastatic breast cancer and multiple myeloma are two of its important causes. Moreover, breast cancer is a predisposing factor for secondary malignancy, multiple myeloma being one of them. We report an interesting case of HCM in which we labelled the first two admissions to metastatic breast cancer. However, on third admission again for HCM, we diagnosed a coexisting multiple myeloma. As early diagnosis is the crux to decrease morbidity and prolong survival in HCM, this case emphasises the fact that more than one malignant cause can exist in the same patient.

BACKGROUND

Hypercalcaemia of malignancy (HCM) is an important cancer-related medical emergency. It is a sign of advanced disease and indicates poor prognosis. Multiple myeloma (MM) and metastatic breast cancer (BC) to bone are known causes of this condition. Also, BC is a predisposing factor for secondary malignancy, MM being one of them. We report an interesting case of HCM in a patient with BC which we thought to be only due to metastatic disease, but a coexisting MM, also contributing to HCM, was detected later.

CASE PRESENTATION

An 86-year-old woman was admitted with decreased sensorium and constipation for 4 days. She was hypertensive for 25 years and on regular treatment. She was diagnosed as having right-sided breast cancer 2 year ago for which modified radical mastectomy was performed and she was then put on aromatase inhibitor. Radiotherapy or chemotherapy was not considered owing to general condition and advance age. On examination, she was thin built, dehydrated, stuporous, irritable and pale. There was no icterus, cyanosis or lymphadenopathy. The vitals of the patient were maintained. On examination of the central nervous system, Glasgow coma scale was E2V2M4, neck rigidity was not present, Babinski's sign was negative and pupils reacted normally. Abdominal examination had palpable fecolith. Rest of the systemic examination was normal. On investigation, she was anaemic (haemoglobin 9.2 g/dL), had hypercalcaemia (16.1 mEq/L; 8.5–10.5 mEq/L), hyperphosphataemia (5.2 mg/dL; 2.4–4 mg/dL) and hyponatraemia (123 mEq/L; 135–145 mEq/L). Her liver and kidney function test (LFT, KFT), total leucocyte count (TLC), chest radiograph, urine examination were within normal limits. A bone scan was performed, which had increased tracer uptake

in manubrium, 8th, 9th and 10th ribs on right side and lumbar vertebra suggesting metastatic disease (figure 1A, B). Her parathyroid hormone and vitamin D3 were normal. Parathyroid hormone-related protein (PTHrP) was not performed as it was not available. She was managed with intravenous saline, furosemide, calcitonin and zoledronic acid infusion and discharged with advice to follow-up in oncology centre.

One month later, she was again admitted with similar symptoms, managed in same line keeping metastatic disease as the cause, and discharged in stable condition. About 3 months after first admission, she was readmitted with gradually increasing pain all over the body for 1 month, cough with expectoration and breathlessness for 15 days, abdomen pain, decreased appetite, constipation for 7 days and decreased sensorium for 2 days. On examination, she was drowsy, irritable, had pain on bone palpation and dehydrated. Blood pressure 110/70 mm Hg, pulse 112/min, temperature 101°F, respiratory rate 24/min, SpO₂ 84% on room air. Chest examination had coarse crackle in left inter-scapular, infrascapular, axial mammary and infra-mammary areas suggestive of pneumonia. There was no focal neurological deficit, and rests of systemic examinations were normal.

INVESTIGATIONS

Investigation revealed anaemia (haemoglobin 8.4 g/dL), with raised TLC (13 400/cc; P88-L10-M2), hypercalcaemia (14.4 mEq/L) and hyperphosphataemia (4.9 mg/dL; 2.4–4 mg/dL); KFT and LFT were normal. Chest radiograph had infiltrates in left middle and lower zone. Typically, serum protein was raised with reversed albumin to globulin ratio (11.9 g/dL; 1:1.84). Radiograph of the skull was taken which had multiple lytic punched out lesions (figure 2), not picked up in bone scan performed 3 months ago. Serum protein electrophoresis showed M spike, and bone marrow aspiration was performed which proved MM with 63% plasma cells. She was in stage 2 of International Staging System (β-2 microglobulin was 3.84 mg/L) and stage 3 of Durie-Salmon staging (serum calcium >12 mg/dL; haemoglobin <8.5 g/dL).

TREATMENT

She was started on intravenous saline, injection calcitonin, zoledronic infusion and antibiotics for pneumonia. Following improvement, first pulse of melphalan and prednisolone was given for 5 days.

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To cite: Trisal D, Kumar N, Sundriyal D, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-204368

Figure 1 (A) Bone scan showing increased tracer uptake in manubrium sternii, 8th, 9th, 10th rib on right side. (B) Bone scan showing increased tracer uptake in posterior part of eighth rib on left, second, third, fourth and fifth lumbar hemivertebrae. There is also lumbar scoliosis.

OUTCOME AND FOLLOW-UP

The patient is doing well, and has completed three cycles of chemotherapy for MM. Her anaemia is better, serum protein reduced to 7.1 g/dL and has not developed hypercalcaemia for past 3 months.

DISCUSSION

Bone pain and new skeletal lesion in a patient with BC is most commonly caused by metastasis to the bone. Apart from local

recurrence, the latter is the most common site for initial metastasis in patients with BC. Bone is involved in 40–75% of patients with metastatic disease.¹

Apart from recurrence, follow-up studies in patients with BC have found increased risk of second malignancy: cancer of ovary, endometrium, lung, colorectal, gall bladder; soft tissue sarcomas; melanomas; leukaemias and lymphomas.^{2–3} Levi *et al*,⁴ in their observational study, calculated the standardised incidence ratio (SIR) of 1.14 for second primary neoplasm in patients of BC. The maximum increase in risk was for soft-tissue sarcomas (SIR-3.20).⁴ Moreover, risk of second malignancy increases with increasing duration from initial diagnosis of BC; Levi *et al*⁴ found that the SIR for second malignancy was 1.04 and 1.25 for breast cancer disease of <5 and ≥5 years duration, respectively. Possible reasons for increased risk of second malignancy following BC are: risk factor predisposing to BC also predisposes to these malignancies; chemotherapy and radiotherapy used to treat BC increase their risk. It has been proved in studies that use of radiotherapy and alkylating agent to treat patients with BC predisposes them to myelodysplasia and leukaemia later in life.³ Plasma cell-related malignancies are uncommon second malignancies in patients with BC.² Levi *et al*⁴ reported only five cases of MM out of 443 second neoplasm in patients with BC (SIR-0.68).⁴

Metastatic BC and MM can present as lytic lesions in the bone. Differentiating the two is important as their management is different with the latter having better prognosis. HCM and anaemia can be present in both of them. Factors that may help in differentiating the two are: site and radiographic features of the lesion, grade and stage of primary, tumour markers. Findings favouring MM are: elevated protein in blood or urine, M spike in serum protein electrophoresis, raised serum free light chain level, skeletal lesion on X-ray with normal bone scan (as lesions are purely osteolytic), low levels of bone alkaline phosphatase (osteoblastic activity), high levels of telopeptide (bone resorption markers) and raised serum β -2 microglobulin. Moreover, metastatic spread from malignancy commonly occurs to axial skeleton and proximal end of the long bone. A lytic lesion in distal appendicular skeleton and small bone of the hands and feet is more common in conditions like MM.

HCM occurs in 10–30% of patients with cancer.⁵ Although it can occur at any stage of the disease, it is often considered as a sign of advanced cancer.⁶ In a study by Ralston *et al*,⁷ median survival from time of detection of HCM was only 30 days, which improved to 135 days with chemotherapy. Hypercalcaemia is defined as serum calcium concentration ≥ 10.5 mg/dL.⁶ It is categorised into three grades of severity: mild, moderate and severe with serum calcium concentrations of 10.5–11.9, 12–13.4 and ≥ 13.5 mg/dL, respectively. HCM is of four types based on the pathogenesis. First is hypercalcaemia of malignancy mediated by PTHrP, known as humoral HCM; it is the most common type accounting for 80% of the cases (eg, squamous cell carcinoma and renal cell carcinoma). Second is HCM caused by osteolysis of bone due to metastasis or direct involvement (20% of cases; eg, metastatic carcinoma breast, multiple myeloma and leukaemia). Rest two are ectopic production of calcitriol by malignancy (eg, lymphomas and ovarian tumours) and ectopic production of PTH. Myeloma is a unique malignancy as it causes pure osteolysis, with majority of patients suffering from progressive bony destruction. It results in hypercalcaemia which remains its most common metabolic complication. Moreover, it is also more common in patients with larger tumour volume and advanced stage of disease. The pathogenesis of HCM associated with metastatic BC with bony

Figure 2 Radiograph of the skull showing multiple punched-out lytic lesions.

involvement is also same, that is, bony resorption with release of calcium. It also correlates with advanced disease.

Our case was interesting in the sense it has two concurrent causes of HCM. With background history of breast cancer, in the first two admissions metastatic disease was kept as the cause of HCM. However, when the patient presented for the third time, we looked for other causes and MM was diagnosed. The

diagnosis was delayed as two conditions had overlapping features. HCM being a life-threatening emergency, we conclude that care should be taken to detect all the causes for proper management of patients. Otherwise it will lead to increased morbidity due to recurrent admissions as in our case.

Contributors DT, NK and DS were involved in the diagnosis and management of the patient, concept of paper, acquiring data, drafting article, revision and final approval of the manuscript. AKG was involved in the diagnosis and management of patient, concept of paper, revision and final approval of the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ The case highlights the importance of investigating a patient in detail on each admission. Superficial or incomplete evaluation should be avoided to reduce the patient's morbidity.
- ▶ In patients with hypercalcaemia of malignancy, more than one malignant cause can exist in the same patient.
- ▶ Skeletal lesion of multiple myeloma cannot be detected on bone scan. It was missed in our case in initial bone scan and was later detected in the skull radiograph.
- ▶ Patients with breast cancer are at increased risk of second malignancy. Risk increases with increasing duration from diagnosis of the primary. Apart from metastasis, they should also be looked for in follow-up.

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